Remarks

Amendments

New claims 29-31 are added. Support for the new claims can be found in the specification at, *inter alia*, page 11, first full paragraph. Claim 1 has been amended for clarity only. Claim 2 has been amended to correct a typographical error. These are not narrowing amendments.

Amendments to the claims are made without prejudice or disclaimer. The amendments are fully supported by the specification as filed and do not introduce new matter. Additionally, these amendments are not and should not be construed as admissions regarding the patentability of the claimed or canceled subject matter. Applicants reserve the right to pursue the subject matter of previously presented claims or any broader claims in this or in any other appropriate patent application. Accordingly, Applicants respectfully request the entry of the amendments presented.

Rejection of Claims 1-5, 7-10, 20 and 26 Under 35 U.S.C. § 112, second paragraph

Claims 1-5, 7-10, 20 and 26 stand as rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse the rejection.

The Office asserts in the Advisory Action of May 13, 2011, that "the limitation after the method step d of 'wherein a polypeptide . . . is isolated' (independent claim 1)" is indefinite because it is not clear if this is a separate method step." This language, however, was deleted from the claims in Applicants' response of December 1, 2010. The claim language is therefore definite.

The Office additionally asserts that method step (a) of claim 1 contains a product-by-process limitation: "that have been grown *in vitro*." The Office appears to assert that the specified phrase represent some sort of "product-by-process" limitation wherein positive method steps must be recited. A product-by-process

claim is a product claim that defines the claimed product in terms of the process by which it is made. *See* MPEP § 2173.05(p). These types of claims are generally considered proper. *Id.* The instant claims are drawn to methods and are therefore not product-by-process claims. As such, the Office's reference to product-by-process claims is unclear.

A claim is definite when those skilled in the art would understand what is claimed when the claim is read in light of the specification. *See Orthokinetics Inc. v. Safety Travel Chairs Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986). Claims must be sufficiently precise to permit a potential competitor to determine whether or not they are infringing. *See Exxon Research and Eng'g Co. v. United States*, 265 F.3d 1371, 1376 (Fed. Cir. 2001).

In order to advance prosecution, claim 1 has been amended to recite a step of "adsorbing the antibody sample with *in vitro* grown cells or cellular extracts of the microbe or pathogen."

The specification teaches that:

> Preferably, a sample containing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro*, such as a serum sample of an infected host, are contacted with *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest, *e.g.* a prokaryotic or eukaryotic cell infected with a virus or parasite.

See specification, page 12, lines 19-21 and working Example 1. Therefore, one of skill in the art, given the specification, would understand that "adsorbing the antibody sample with *in vitro* grown cells or cellular extracts of the microbe or pathogen" can be, *e.g.*, *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest.

The method claims of the invention recite proper positive steps using well-defined compositions and reagents. Therefore, one of skill in the art would understand what is claimed when the claim is read in light of the specification.

The claims as presented herein are definite and Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-5, 7-10, 20, and 26 Under 35 U.S.C. § 103(a)

Claims 1-5, 7-10, 20, and 26 stand as rejected under 35 U.S.C. § 103(a), as allegedly obvious over Bickel *et al.* WO98/30910 and Suk *et al.* Applicants respectfully traverse the rejection.

The Office asserts in the Advisory Action of May 13, 2011, that Suk *et al.* teach collecting sera from mice infected with *B. burgdorferi* and Bickel *et al.* teaches immunodepletion methods. However, Suk *et al.* teaches that the mice were not naturally infected with *B. burgdorferi* as required by the claims. Rather, the mice of Suk were intradermally injected with *B. burgdorferi* by researchers. *See* Suk page 4269, right col. No animals or humans need to be injected with pathogens according the methods of the invention. A major drawback of animal models or models that are not naturally infected is that the model may not closely approximate the naturally-infected host or human condition. In fact, "a number of examples exist in the literature of erroneous conclusions being drawn by extrapolation of results from animal models to human infections." *See* Handfield *et al.,* Trends in Microbiol. 8:336 (2000), page 336, left col; *see also*, specification page 2, first full paragraph.

Additionally, Bickel teaches only the non-natural immunization of animals with cellular proteins and does not teach infection with live organisms. Bickel does not teach or suggest "obtaining an antibody sample from one or more hosts naturally infected with the microbe or pathogen" of the claims. The abstract of Bickel states that "[t]he immunodepleted antiserum is raised against a particular cell type of interest or subcellular fraction of a particular cell type of interest, and depleted of antibodies that bind antigens from at least one other cell type or subcellular fraction of at least one other cell type." The Office has asserted that this teaches an antibody sample from one or more hosts infected with a microbe or pathogen. Bickel, however, is very clear that the antiserum raised against a particular cell type is "antiserum produced by immunizing a suitable host with **proteins derived** from the cell type of interest." *See* page 5, lines 5-8 (emphasis added). Figure 1 of Bickel states that their method includes "immuniz[ing a] host with target proteins." Additionally, page 12, lines 24-28, states that "[p]olyclonal

antiserum is prepared against proteins of the target cells according to known methods." Nowhere does Bickel teach or suggest that a **whole, infective** microbe or pathogen would be used to immunize or naturally infect the host. It appears the abstract of Bickel is differentiating between antiserum that is raised against all proteins of particular cell type of interest and antiserum that is raised against only a subcellular fraction of proteins of particular cell type of interest.

Furthermore, the claims require "obtaining an antibody sample from one or more hosts naturally infected with the microbe or pathogen." Bickel does not teach or suggest obtaining an antibody sample from a naturally infected host, but from a host immunized with proteins obtained from a particular cell type. The methods of the invention require the use of an antibody sample from a host that has been naturally infected with an infectious pathogen or microbe. An animal model or a surrogate *in vitro* system is not required by the methods of the invention. It is well established that microbial infections are complex, dynamic processes that evolve constantly within the host, and that virulence gene expression is modulated in response to the changing environment encountered at the site of infection. *See* Handfield *et al.* Trends Microbiol. 8:336 (2000) (of record). Therefore, all regulated virulence determinants of a host pathogen, such as a human pathogen cannot be identified *in vitro* or in an animal model of infection because it is technically impossible to determine and mimic all of the complex and changing environmental stimuli that occur at the site of an actual host infection, such as a human infection, and reproduce them in an animal model of infection. Work performed using the methods of Bickel would necessarily miss those critical virulence determinants that are specifically induced in infected hosts, such as infected humans.

Applicants note that the proteins of Bickel could not be considered to be "a pathogen." The instant specification defines a microbe or pathogen as any kind of a bacterium, a virus, a parasite, a prion, or a fungus. As such, the proteins used for immunization in Bickel are not pathogens as defined by the instant invention.

To support an obviousness rejection, MPEP §2143.03 requires "all words of a claim to be considered" and MPEP § 2141.02 requires consideration of the "[claimed] invention and prior art as a whole." Further, the Board of Patent Appeal and Interferences confirmed that a proper, post-KSR obviousness determination still requires the Office make "a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art." *In re Wada and Murphy*, Appeal 2007-3733, citing *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) and *CFMT v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003); *See also Honeywell Intn'l v. U.S.*, 609 F.3d 1292, 1300 (Fed. Cir. 2010).

In sum, it remains well-settled law that an obviousness rejection requires at least a suggestion of *all* of the claim elements. Because the obviousness rejection ignores the claim 1 element of "obtaining an antibody sample from one or more hosts naturally infected with the microbe or pathogen" the obviousness rejection is improper.

Neither Bickel nor Suk, alone or in combination, teach an essential element of the invention: the use of a host that was naturally infected with a pathogen. As such, this combination of references cannot render the invention obvious.

Furthermore, with reference to claim 26, neither Bickel nor Suk, alone or in combination, teach or suggest that the naturally infected host can be a human. Bickel used rabbit hosts (see Example 1) and Suk used mice hosts (see page 4269, right col.).

With reference to new claim 29, animal models may be limited to only one route of infection of the pathogen. Suk only intradermally injected *B. burgdorferi* into mice (*see* page 4269, right col.). The methods of the invention can analyze multiple infection routes of a pathogen simultaneously. Bickel and Suk, alone or in combination, do not teach or suggest the simultaneous analysis of multiple routes of infection of a pathogen.

With reference to new claim 30, animal models may be limited to only one phase of infection by the pathogen. The mice of Suk were injected with *B.*

burgdorferi and then all sacrificed after 9 months (*see* page 4269, right col.). All mice were therefore in the same phase of infection. The methods of the invention can analyze multiple infection phases of a pathogen simultaneously. Bickel and Suk, alone or in combination, do not teach or suggest the simultaneous analysis of multiple phases of infection of a pathogen.

With reference to new claim 31, animal models may be limited to only one strain or clonal type of the pathogen. Suk injected one strain of *B. burgdorferi* into mice (*see* page 4269, right col.). The methods of the invention can analyze multiple strains and clonal types simultaneously. Bickel and Suk, alone or in combination, do not teach or suggest the simultaneous analysis of multiple strains and clonal types.

The instant invention requires hosts that are naturally infected with pathogens. This provides direct relevance to the natural host of the pathogen. Bickel and Suk, alone or in combination, do not teach or suggest the methods of the invention. Applicants respectfully request withdrawal of the rejection.

References Cited in Advisory Action

The Examiner cites several references on page 3 of the Advisory Action issued on 5/13/11, and has made the references of record. The Office, however, did not apply these references in rejecting the claims. Applicants disagree with the Office's general contention that these references are pertinent to Applicants' disclosure in this application. Unless the connection between the references and the present application is explained, Applicants urge the Office to withdraw these contentions from the record.

Respectfully submitted,

Dated: June 14, 2011 By: /Lisa M.W. Hillman/
Lisa M.W. Hillman, Ph.D.
Registration No. 43,673
217-239-1962